

Neonatal Diseases

The human genome is often referred to as a "blueprint" and contains all of the information and instructions necessary for defining a human being. The term genome refers collectively to the DNA and associated protein molecules contained in an organism or a cell. The human genome consists of 23 pairs of chromosomes — threadlike packages of genes and other DNA — with each parent contributing one chromosome to each pair.

A gene is a specific sequence of DNA and is actually the functional unit of inheritance. Most genes contain the information needed to make a protein, or molecules that carry out all of a cell's vital activities. Therefore, slight variations in genes lead to slight changes in a protein. Although some human diseases are explained by alterations in a single gene or of a single chromosome, most are complex and may involve multiple genes and protein pathways.

A myriad of genes, as well as environmental factors, are believed to control the complex and integrated processes necessary for fetal development. When one or more of these processes goes awry, it can result in the birth of an individual with a genetic alteration. Scientific studies, often those that use other organisms as a model, will provide information about biological and regulatory processes involved in human development and will identify critical pathways in which genetic changes result in disease. This information will come not only from human studies, but also from other model organisms — such as mouse or yeast — that can provide insights into how key genes operate in complex systems.

Achondroplasia

Achondroplasia is a Greek word meaning "without cartilage formation" and is one of the most common causes of dwarfism. The appearance is of short stature with disproportionately short arms and legs and a large head. The characteristic facial features include a prominent forehead and a flattened bridge of the nose.

Although this condition can be inherited in an autosomal dominant manner, 80% of cases are due to new, sporadic mutations. Mutations involve the gene encoding fibroblast growth factor receptor 3 (FGFR3), situated on chromosome 4. Most commonly, a point mutation causes the substitution of arginine for glycine (G380R) in the transmembrane region of the receptor.

There is growing evidence that mutations of FGFR3 confer a "gain of function". It is proposed that the normal function of FGFR3 is to slow down the formation of bone by inhibiting the proliferation of chondrocytes, the cells that produce cartilage. The mutation increases the activity of FGFR3, severely limiting bone growth.

This theory is supported by the knock-out mouse model in which the receptor is absent, and so the negative regulation of bone formation is lost. The result is a mouse with excessively long bones and elongated vertebrae, resulting in a long tail. Achondroplastic mouse models are useful tools in developing potential treatments.



Achondroplasia. This girl has disproportionate shortening of the limbs that is more marked in the upper arms and upper legs (rhizomelic shortening). She also has a prominent forehead (frontal bossing) and depressed nasal bridge.

[Image credit: Jorde, Carey, Bamshad, White; Medical Genetics 2nd Edition © 1999, with permission from Elsevier.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=achondroplasia] see gene locations
LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=achondroplasia&ORG=Hs&V=0] collection of gene-related information
Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=20452381&org=1] related sequences in different organisms

The literature

Research articles [http://www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=achondroplasia%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=achondroplasia] online books section
OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=100800] catalog of human genes and disorders

Websites

Genes and Disease

Achondroplasia UK [www.achondroplasia.co.uk/] support and patient information

Little People of America [www.lpaonline.org/index.html] support and information for families

GeneReviews [www.genetests.org/profiles/achondroplasia] a medical genetics resource

Neonatal Diseases

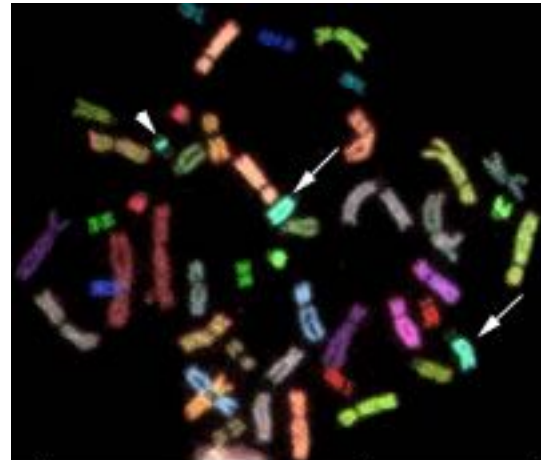
Angelman Syndrome

Angelman syndrome (AS) is an uncommon neuro-genetic disorder characterized by mental retardation, abnormal gait, speech impairment, seizures, and an inappropriate happy demeanor that includes frequent laughing, smiling, and excitability. The uncoordinated gait and laughter have caused some people to refer to this disorder as the "happy puppet" syndrome.

The genetic basis of AS is very complex, but the majority of cases are due to a deletion of segment 15q11–q13 on the maternally derived chromosome 15. When this same region is missing from the paternally derived chromosome, an entirely different disorder, Prader–Willi syndrome, results. This phenomenon—when the expression of genetic material depends on whether it has been inherited from the mother or the father—is termed genomic imprinting.

The ubiquitin ligase gene (UBE3A) is found in the AS chromosomal region. It codes for an enzyme that is a key part of a cellular protein degradation system. AS is thought to occur when mutations in UBE3A disrupt protein break down during brain development.

In a mouse model of AS, affected animals had much less maternally inherited UBE3A than their unaffected litter mates. However, this difference in UBE3A levels was only found in the hippocampus and the cerebellum, and not all of the brain. This animal model and other molecular techniques are helping us learn more about the disparate maternal and paternal expression of the UBE3A gene.



Chromosome painting techniques such as M-FISH tint each pair of the 24 human chromosomes a different color. This allows the fragment (arrow head) to be identified as an extra piece of chromosome 15, since it is the same aqua color as the two normal copies of chromosome 15 (arrows). This technique may help in the diagnosis of genetic disorders that arise from chromosomal changes too subtle for conventional techniques.

[Reproduced with permission from Uhrig, S. et al. (1999) Multiplex-FISH for pre- and postnatal diagnostic applications. *Am J Hum Genet.* Aug; 65(2): 448-62, published by the University of Chicago Press, copyright 1999 by the American Society for Human Genetics. All rights reserved.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=angelman] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=angelman&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4507799&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=angelman%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=angelman] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=105830] catalog of human genes and disorders

Websites

Angelman Syndrome Foundation, USA [chem-faculty.ucsd.edu/harvey/asfsite/] provides information, education and support
 GeneClinics [www.geneclinics.org/profiles/angelman/] a medical genetics resource

Cockayne Syndrome

Edward Alfred Cockayne (1880–1956), after whom this disease is named, was a London physician who concentrated particularly on hereditary diseases of children. Cockayne syndrome is a rare inherited disorder in which people are sensitive to sunlight, have short stature, and have the appearance of premature aging. In the classical form of Cockayne syndrome (Type I), the symptoms are progressive and typically become apparent after the age of 1 year. An early onset or congenital form of Cockayne syndrome (Type II) is apparent at birth. Interestingly, unlike other DNA repair diseases, Cockayne syndrome is not linked to cancer.

After exposure to UV radiation (found in sunlight), people with Cockayne syndrome can no longer perform a certain type of DNA repair, known as "transcription-coupled repair." This type of DNA repair occurs "on the fly" right as the DNA that codes for proteins is being replicated. Two genes defective in Cockayne syndrome, CSA and CSB, have been identified so far. The CSA gene is found on chromosome 5. Both genes code for proteins that interact with components of the transcriptional machinery and with DNA repair proteins.

Escherichia coli, a bacterium, also undergoes transcription-coupled repair, and a yeast counterpart of the CSB gene has also recently been discovered. These similar mechanisms to the one found in humans are invaluable for studying the molecular processes involved in transcription-coupled repair because powerful molecular genetics techniques can be used. A better understanding of the mechanisms involved will help unravel the pathogenesis of disease and may identify potential drug targets.



Cockayne syndrome sufferers have multi-systemic disorders due to a defect in the ability of cells to repair DNA that is being transcribed. [Photograph by D. Atherton. Reproduced from Lehmann, A.R. (1995) Trends Biochem. Sci. 20, 402-405, with permission.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=cockayne] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=cockayne&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557467&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=cockayne%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=cockayne] online books section

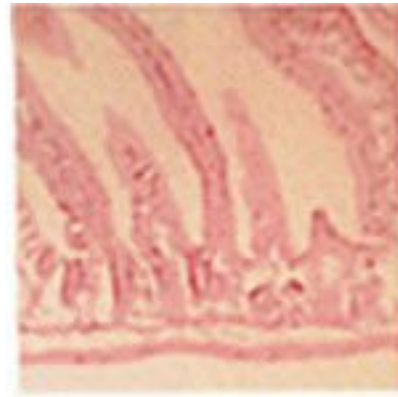
OMIM [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=cockayne] catalog of human genes and disorders

Cystic Fibrosis

Cystic fibrosis (CF) is the most common fatal genetic disease in the US today. It causes the body to produce a thick, sticky mucus that clogs the lungs, leading to infection, and blocks the pancreas, stopping digestive enzymes from reaching the intestines where they are required to digest food.

CF is caused by a defective gene, which codes for a sodium and chloride (salt) transporter found on the surface of the epithelial cells that line the lungs and other organs. Several hundred mutations have been found in this gene, all of which result in defective transport of sodium and chloride by epithelial cells. The severity of the disease symptoms of CF is directly related to the characteristic effects of the particular mutation(s) that have been inherited by the sufferer.

CF research has accelerated sharply since the discovery of CFTR in 1989. In 1990, scientists successfully cloned the normal gene and added it to CF cells in the laboratory, which corrected the defective sodium chloride transport mechanism. This technique—gene therapy—was then tried on a limited number of CF patients. However this treatment may not be as successful as originally hoped. Further research will be required before gene therapy, and other experimental treatments, prove useful in combating CF.



Building mouse models of human disease. Expression of a human cystic fibrosis (CFTR) gene in the gut of a mouse. A human anti-sense probe was used to show human CFTR expressed in the mouse duodenum. [Reproduced with permission from Manson, A.L. et al. (1997) *EMBO J.* 16, 4238-4249.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=cystic%20fibrosis] see gene locations
LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=cystic%20fibrosis&ORG=Hs&V=0] collection of gene-related information
Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=6995996&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=cystic%20fibrosis%20AND%20%22pubmed%20PMC%22%5BFilter%5D] online full text
Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=cystic%20fibrosis] online books section
OMIM [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=cystic%20fibrosis] catalog of human genes and disorders

Websites

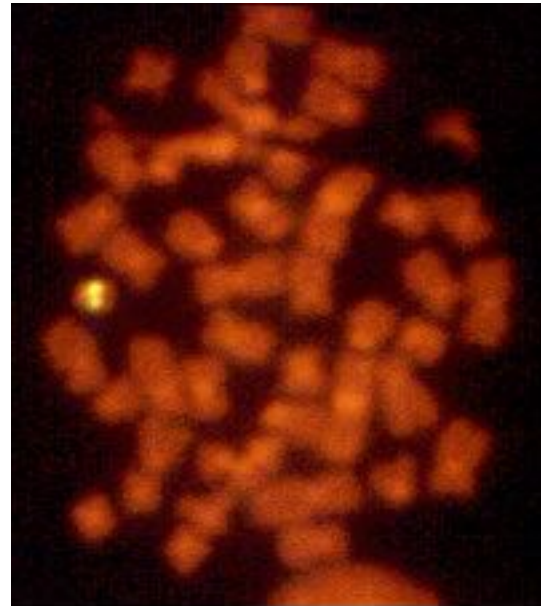
Fact sheet [www.nhlbi.nih.gov/health/public/lung/other/cystfib.htm] from the National Heart, Lung and Blood Institute, NIH
The Cystic Fibrosis Foundation [www.cff.org/] information and links

DiGeorge Syndrome

DiGeorge syndrome is a rare congenital (i.e. present at birth) disease whose symptoms vary greatly between individuals but commonly include a history of recurrent infection, heart defects, and characteristic facial features.

DiGeorge syndrome is caused by a large deletion from chromosome 22, produced by an error in recombination at meiosis (the process that creates germ cells and ensures genetic variation in the offspring). This deletion means that several genes from this region are not present in DiGeorge syndrome patients. It appears that the variation in the symptoms of the disease is related to the amount of genetic material lost in the chromosomal deletion.

Although researchers now know that the DGS gene is required for the normal development of the thymus and related glands, counteracting the loss of DGS is difficult. Some effects, for example the cardiac problems and some of the speech impairments, can be treated either surgically or therapeutically, but the loss of immune system T-cells (produced by the thymus) is more challenging and requires further research on recombination and immune function.



Deletion of genes in DiGeorge syndrome can be visualized by a fluorescent signal on only one of the two copies of chromosome 22. [Image credit: David Ian Wilson, University of Newcastle upon Tyne, UK.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=DiGeorge] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=DiGeorge&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=13027630&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=DiGeorge%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=DiGeorge] online books section

OMIM [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=omim&details_term=DiGeorge] catalog of human genes and disorders

Websites

Information and support [www.kumc.edu/gec/support/digeorge.html] for DiGeorge syndrome

GeneClinics [www.geneclinics.org/profiles/22q11deletion/] a medical genetics resource

Fragile X Syndrome

Fragile X syndrome is the most common inherited form of mental retardation currently known. Fragile X syndrome is a defect in the X chromosome and its effects are seen more frequently, and with greater severity, in males than females.

In normal individuals, the FMR1 gene is transmitted stably from parent to child. However, in Fragile X individuals, there is a mutation in one end of the gene (the 5' untranslated region), consisting of an amplification of a CGG repeat. Patients with fragile X syndrome have 200 or more copies of the CGG motif. The huge expansion of this repeat means that the FMR1 gene is not expressed, so no FMR1 protein is made. Although the exact function of FMR1 protein in the cell is unclear, it is known that it binds RNA.

A similar nucleotide repeat expansion is seen in other diseases, such as Huntington disease. Research in mice has proven helpful in elucidating some of the mechanisms that cause the instability of this gene. Our methods for identifying carriers of Fragile X syndrome have also improved, and further research will help people carrying "premutations" to avoid having children who have a larger expansion (i.e. more CGG repeats) in FMR1, and therefore suffer from Fragile X syndrome.



An unstable nucleotide repeat is associated with the most common form of mental retardation known as Fragile X syndrome.
[Image credit: Steve Warren, Emory University School of Medicine, Atlanta, GA, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=Fragile+X] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=Fragile+X&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4503765&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=Fragile+X%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=Fragile+X] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=309550] catalog of human genes and disorders

Websites

Fact sheet [www.nichd.nih.gov/publications/pubs/fragilextoc.htm] from the National Institute of Child Health and Human Development, NIH

National Fragile X Foundation [www.fragilex.org] US-based research, information and support

GeneClinics [www.geneclinics.org/profiles/fragilex/] a medical genetics resource

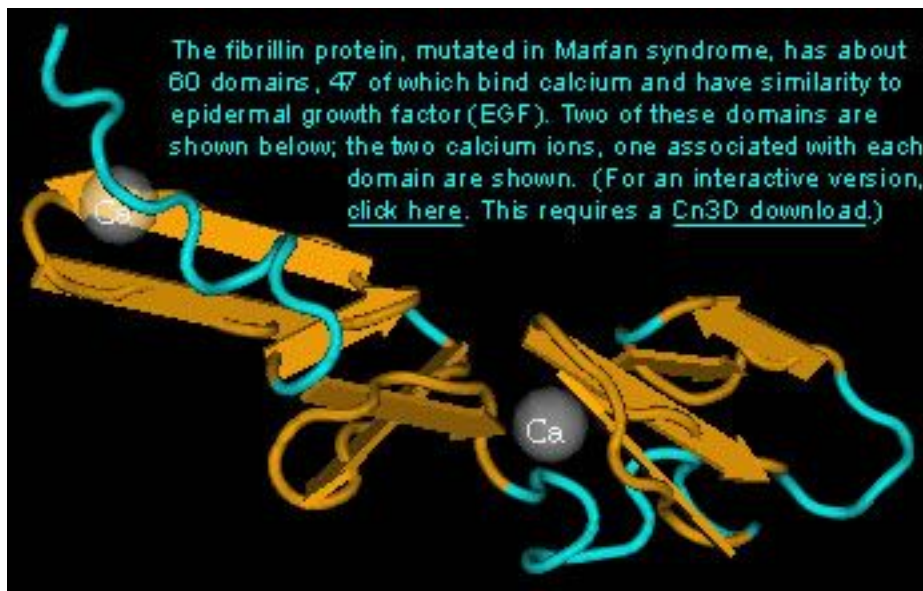
Marfan Syndrome

Marfan syndrome is a connective tissue disorder, so affects many structures, including the skeleton, lungs, eyes, heart and blood vessels. The disease is characterized by unusually long limbs, and is believed to have affected Abraham Lincoln.

Marfan syndrome is an autosomal dominant disorder that has been linked to the *FBN1* gene on chromosome 15. *FBN1* encodes a protein called fibrillin, which is essential for the formation of elastic fibres found in connective tissue. Without the structural support provided by fibrillin, many tissues are weakened, which can have severe consequences, for example, ruptures in the walls of major arteries.

Beta blockers have been used to control some of the cardiovascular symptoms of Marfan syndrome; however, they are not effective against the skeletal and ocular problems, which can also be serious. A related disease has been found in mice, and it is hoped that the study of mouse fibrillin synthesis and secretion, and connective tissue formation, will further our understanding Marfan syndrome in humans.

To see the interactive version of this figure requires Cn3D [www.ncbi.nlm.nih.gov/Structure/CN3D/cn3d.shtml], a three-dimensional structure viewer.



Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=marfan] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=marfan&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557591&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=marfan%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=marfan] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=154700] catalog of human genes and disorders

Websites

National Marfan Foundation [www.marfan.org/] nonprofit organization

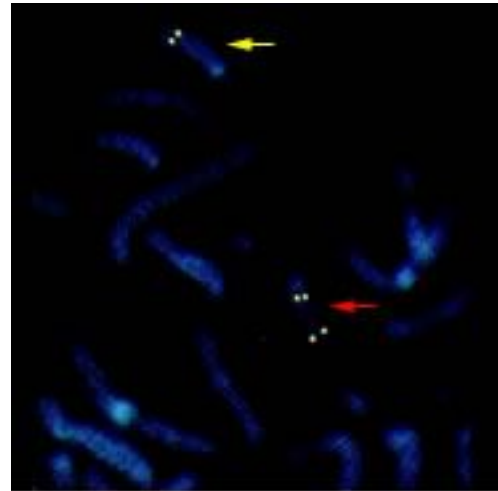
Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is an uncommon inherited disorder characterized by mental retardation, decreased muscle tone, short stature, emotional lability and an insatiable appetite which can lead to life-threatening obesity. The syndrome was first described in 1956 by Drs. Prader, Labhart, and Willi.

PWS is caused by the absence of segment 11-13 on the long arm of the paternally derived chromosome 15. In 70-80% of PWS cases, the region is missing due to a deletion. Certain genes in this region are normally suppressed on the maternal chromosome, so, for normal development to occur, they must be expressed on the paternal chromosome. When these paternally derived genes are absent or disrupted, the PWS phenotype results. When this same segment is missing from the maternally derived chromosome 15, a completely different disease, Angelman syndrome, arises. This pattern of inheritance — when expression of a gene depends on whether it is inherited from the mother or the father — is called genomic imprinting. The mechanism of imprinting is uncertain, but, it may involve DNA methylation.

Genes found in the PWS chromosomal region code for the small ribonucleoprotein N (SNRPN). SNRPN is involved in mRNA processing, an intermediate step between DNA transcription and protein formation. A mouse model of PWS has been developed with a large deletion which includes the SNRPN region and the PWS 'imprinting centre' (IC) and shows a phenotype similar to infants with PWS.

These and other molecular biology techniques may lead to a better understanding of PWS and the mechanisms of genomic imprinting.



In the Prader-Willi syndrome (PWS) cell above, the maternally derived chromosome 15 (red arrow) shows two signals: one from a control area (which is also seen in the paternally derived chromosome [yellow arrow]) and another, which is from the PWS region. This signal is missing from the paternal chromosome because the region is deleted in this PWS patient. [Reproduced with permission from Martin et al. (1998) *Am J Psychiatry* Sep;155(9):1265-73.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=prader-willi] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=prader-willi&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=14748674&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=prader-willi%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=prader-willi] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=176270] catalog of human genes and disorders

Websites

Prader-Willi Syndrome Association (USA) [www.pwsausa.org/] information, education, and support services
 GeneClinics [www.geneclinics.org/profiles/pws/] a medical genetics resource

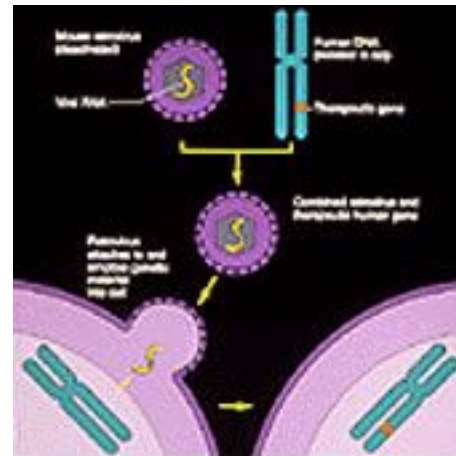
Severe Combined Immunodeficiency

Severe combined immunodeficiency (SCID) represents a group of rare, sometimes fatal, congenital disorders characterized by little or no immune response. The defining feature of SCID, commonly known as "bubble boy" disease, is a defect in the specialized white blood cells (B- and T-lymphocytes) that defend us from infection by viruses, bacteria and fungi. Without a functional immune system, SCID patients are susceptible to recurrent infections such as pneumonia, meningitis and chicken pox, and can die before the first year of life. Though invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients.

All forms of SCID are inherited, with as many as half of SCID cases linked to the X chromosome, passed on by the mother. X-linked SCID results from a mutation in the interleukin 2 receptor gamma (IL2RG) gene which produces the common gamma chain subunit, a component of several IL receptors. IL2RG activates an important signalling molecule, JAK3. A mutation in JAK3, located on chromosome 19, can also result in SCID. Defective IL receptors and IL receptor pathways prevent the proper development of T-lymphocytes that play a key role in identifying invading agents as well as activating and regulating other cells of the immune system.

In another form of SCID, there is a lack of the enzyme adenosine deaminase (ADA), coded for by a gene on chromosome 20. This means that the substrates for this enzyme accumulate in cells. Immature lymphoid cells of the immune system are particularly sensitive to the toxic effects of these unused substrates, so fail to reach maturity. As a result, the immune system of the afflicted individual is severely compromised or completely lacking.

Some of the most promising developments in the search for new therapies for SCID center on 'SCID mice', which can be bred deficient in various genes including ADA, JAK3, and IL2RG. It is now possible to reconstitute the impaired mouse immune system by using human components, so these animals provide a very useful model for studying both normal and pathological immune systems in biomedical research.



Gene therapy has been attempted to treat severe combined immunodeficiency caused by a missing enzyme, adenosine deaminase. [Image credit: National Cancer Institute.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=SCID] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=SCID&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4557681&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=SCID%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=SCID] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=202500] catalog of human genes and disorders

Websites

SCID Factsheet [www.niaid.nih.gov/factsheets/pid.htm] from the National Institute of Allergy and Infectious Diseases, National Institutes of Health

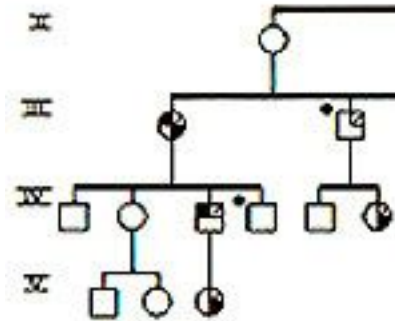
Waardenburg Syndrome

The main characteristics of Waardenburg syndrome (WS) include: a wide bridge of the nose; pigmentary disturbances such as two different colored eyes, white forelock and eyelashes and premature graying of the hair; and some degree of cochlear deafness. The disease was named for Petrus Johannes Waardenburg, a Dutch ophthalmologist (1886-1979) who was the first to notice that people with two different colored eyes frequently had hearing problems.

The several types of WS are inherited in dominant fashion, so researchers typically see families with several generations who have inherited one or more of the features. Type I of the disorder is characterized by displacement of the fold of the eyelid, while Type II does not include this feature, but instead has a higher frequency of deafness.

The discovery of the human gene that causes Type I WS came about after scientists speculated that the gene that causes 'splotch mice' (mice with a splotchy coat coloring) might be the same gene that causes WS in humans. They located the human gene to chromosome 2 and found it was the same as mouse Pax3. Pax3 is one of a family of eight mouse Pax genes that are involved in regulating embryonic development at the level of transcription.

With a mouse model to draw from, scientists are learning much about how Pax3 causes Waardenburg syndrome.



Part of a pedigree of Waardenburg syndrome, indicating the occurrence of deafness and changes in pigmentation, including a white forelock. [Image credit: Victor McKusick, Johns Hopkins University, Baltimore, MD, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=waardenburg] see gene locations
 LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=waardenburg&ORG=Hs&V=0] collection of gene-related information
 Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=6654638&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=waardenburg%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text
 Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=waardenburg] online books section
 OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=193500] catalog of human genes and disorders

Websites

Search [www.aerie.com/nihdb/nidcd/dctest.html] the National Institute for Deafness and other Communication Disorders, NIH
 The Boys Town Research Registry for Hereditary Hearing Loss [www.boystown.org/hhrr/] fostering links between families, clinicians and researchers

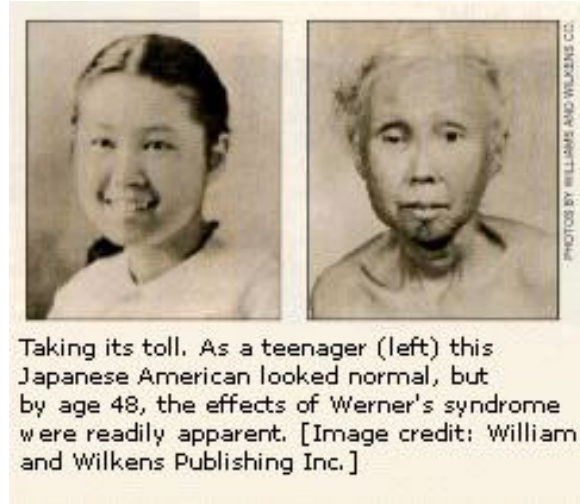
Werner Syndrome

Werner syndrome is a premature aging disease that begins in adolescence or early adulthood and results in the appearance of old age by 30-40 years of age. Its physical characteristics may include short stature (common from childhood on) and other features usually developing during adulthood: wrinkled skin, baldness, cataracts, muscular atrophy and a tendency to diabetes mellitus, among others.

The disorder is inherited and transmitted as an autosomal recessive trait. Cells from WS patients have a shorter lifespan in culture than do normal cells. The gene for Werner disease (WRN) was mapped to chromosome 8 and cloned: by comparing its sequence to existing sequences in GenBank, it is a predicted helicase belonging to the RecQ family. However, it has yet to be shown to have real helicase activity (as a DNA unwinder important for DNA replication). The molecular role of WRN in Werner syndrome therefore remains to be proven, as does any role it might have in the aging process in general.

A yeast protein similar to the human WRN protein, called SGS1, has been found. Mutations in SGS1 cause yeast to have a shorter lifespan than

yeast cells without the mutation, and shown other signs typical of aging in yeast, such as an enlarged and fragmented nucleolus. Using yeast as a model for human aging in general, may give insight into the mechanisms of Werner syndrome and related diseases.



Taking its toll. As a teenager (left) this Japanese American looked normal, but by age 48, the effects of Werner's syndrome were readily apparent. [Image credit: William and Wilkens Publishing Inc.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=WRN] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=WRN&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5739524&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=WRN%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=WRN] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=277700] catalog of human genes and disorders

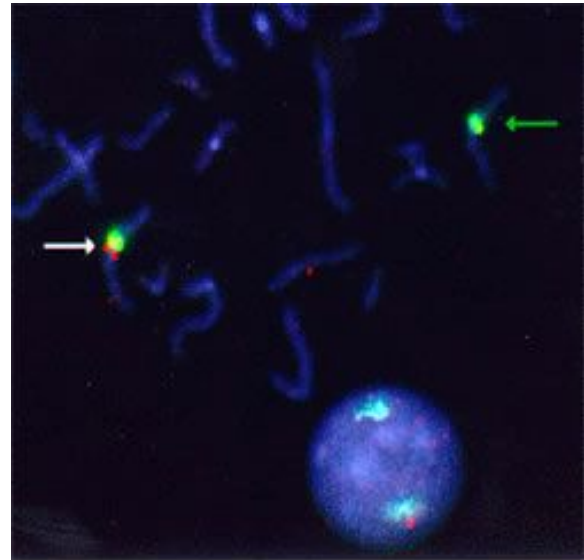
Williams Syndrome

Williams syndrome is a rare congenital disorder characterized by physical and development problems. Common features include characteristic "elfin-like" facial features, heart and blood vessel problems, irritability during infancy, dental and kidney abnormalities, hyperacusis (sensitive hearing) and musculoskeletal problems. Although individuals with Williams syndrome may show competence in areas such as language, music and interpersonal relations, their IQs are usually low.

In Williams syndrome individuals, both the gene for elastin and an enzyme called LIM kinase are deleted. Both genes map to the same small area on chromosome 7. In normal cells, elastin is a key component of connective tissue, conferring its elastic properties. Mutation or deletion of elastin lead to the vascular disease observed in Williams syndrome. On the other hand, LIM kinase is strongly expressed in the brain, and deletion of LIM kinase is thought to account for the impaired visuospatial constructive cognition in Williams syndrome.

Williams syndrome is a contiguous disease, meaning that the deletion of this section of chromosome 7 may involve several more genes. Further study will be required to round up all the genes deleted in this disease. The remarkable musical and verbal abilities of individuals with Williams syndrome, and their tendency to be very sociable, has lead to the suggestion that children with Williams

syndrome were an inspiration for folktales and legends, as the 'wee, magical people' were often musicians and storytellers.



Williams syndrome is caused by a deletion of part of chromosome 7 that includes the LIM kinase and elastin coding sequences. Above, this sequence (stained red) can no longer be seen in the chromosome with the deletion (green arrow). [Photograph kindly provided by L. G. Shaffer, Baylor College of Medicine.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=LIM%20kinase%20OR%20elastin] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=LIM%20kinase%20OR%20elastin&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=5881413&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=LIM%20kinase%20OR%20elastin%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=LIM%20kinase%20OR%20elastin] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispmim.cgi?id=194050] catalog of human genes and disorders

Websites

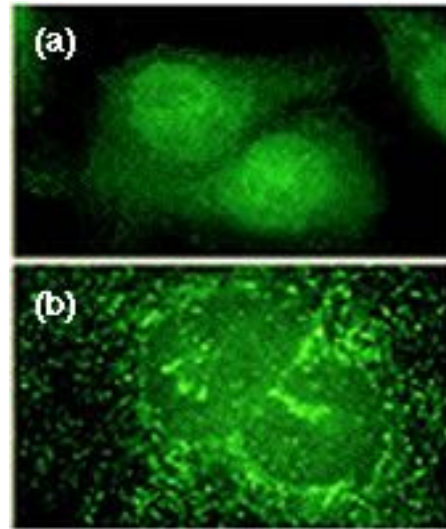
GeneClinics [www.geneclinics.org/profiles/williams/] a medical genetics resource

Zellweger Syndrome

Zellweger syndrome is a rare hereditary disorder affecting infants, and usually results in death. Unusual problems in prenatal development, an enlarged liver, high levels of iron and copper in the blood, and vision disturbances are among the major manifestations of Zellweger syndrome.

The PXR1 gene has been mapped to chromosome 12; mutations in this gene cause Zellweger syndrome. The PXR1 gene product is a receptor found on the surface of peroxisomes - microbodies found in animal cells, especially liver, kidney and brain cells. The function of peroxisomes is not fully understood, although the enzymes they contain carry out a number of metabolically important reactions. The PXR1 receptor is vital for the import of these enzymes into the peroxisomes: without it functioning properly, the peroxisomes can not use the enzymes to carry out their important functions, such as cellular lipid metabolism and metabolic oxidations.

There is a yeast homolog to human PXR1, which should allow powerful molecular genetic techniques to be used in the investigation of the normal role of peroxisomes in cells, as well as the molecular events that occur in disease states.



Peroxisomes are not detected in Zellweger syndrome fibroblasts (a), but can be reconstituted by transfection with PXR1 gene (b). [Image credit: Nancy Braverman, Gabrielle Dodt, Hugo Moser, Stephen Gould and David Valle, Johns Hopkins University, Baltimore, MD, USA.]

Important Links

Gene sequence

Genome view [www.ncbi.nlm.nih.gov/mapview/map_search.cgi?chr=hum_chr.inf&query=zellweger] see gene locations

LocusLink [www.ncbi.nlm.nih.gov/LocusLink/list.cgi?Q=zellweger&ORG=Hs&V=0] collection of gene-related information

Blink [www.ncbi.nlm.nih.gov/sutils/blink.cgi?pid=4506347&org=1] related sequences in different organisms

The literature

Research articles [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=PubMed&details_term=zellweger%20AND%20%22pubmed%20pmc%22%5BFilter%5D] online full text

Books [www.ncbi.nlm.nih.gov/80/entrez/query.fcgi?cmd=PureSearch&db=books&details_term=zellweger] online books section

OMIM [www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=600414] catalog of human genes and disorders

Websites

Fact sheet [www.ninds.nih.gov/health_and_medical/disorders/zellwege_doc.htm] from the National Institute of Neurological Disorders and Stroke, NIH